REMARKS

Claims 168, 167, 184, 198, 211, and 212 are amended to more clearly reflect the claimed material. Claims 154-168, 170-181, 184-198, 200-212, and 215-216 are pending in the present application. The material disclosed in claims 215 and 216 was previously disclosed in claim 212 and therefore no new matters is added thereby. Specifically, each of the kit reagents (namely the antigen, the non-immobilized antibody providing the detection means and the immobilized antibody) are specified as being provided on the substrate of the kit.

Claims 154-168, 170-181, and 211-212 are rejected under 35 U.S.C. § 103(a) as obvious over Bergman (U.S. Pat. No. 5,501,955) in view of Ehrenkranz (WO 96/27129) and May et al. (U.S. Pat. No. 5,622,871). Claims 184-198 and 200-210 are rejected under 35 U.S.C. § 103(a) as obvious over Bergman in view of Ehrenkranz and May et al. as applied to claims 154-168, 170-181, and 211-212, and further in view of Foster et al. (U.S. Pat. No. 4,444,879). Applicant respectfully traverses these rejections and submits that the claims are not obvious in light of the cited references.

To make out a *prima facie* case of obviousness under 35 U.S.C. § 103(a), there must exist some motivation, either generally available to one of ordinary skill in the art or expressly stated in the prior art, to modify the known prior art to arrive at the claimed invention. For a 35 U.S.C. § 103(a) rejection, the examiner should set forth the following in the Office Action:

(A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,

(B) the difference or differences in the claim over the applied reference(s),

(C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and

(D) an explanation why one of ordinary skill in the art at the time the invention was made would have been motivated to make the modification.

M.P.E.P. § 706.02(j) (2003).

Rejection of Claims 168, 170-181, 198, and 200-210 under 35 U.S.C. § 103(a)

Claims 168 and 170-181 are rejected under 35 U.S.C. § 103(a) as obvious over Bergman (U.S. Pat. No. 5,501,955) in view of Ehrenkranz, and May et al. Claims 198 and 200-210 are rejected under 35 U.S.C. § 103(a) as obvious over Bergman in view of Ehrenkranz, and May et al. as applied to claims 154-168, 170-181, and 211-212, and further in view of Foster et al.

Amended independent claims 168 and 198 represent method and kit claims respectively, which employ an immobilized antibody, a mobile labeled antibody, and a mobile antigen with first and second binding sites for the respective antibodies. Claims 170-181 are dependent on claim 168, and claims 200-210 are dependent on claim 198. This embodiment allows synchronous binding of first and second autoantibodies to distinct binding sites of the antigen, i.e., to the first and second binding site of the mobile antigen.

In Bergman, reference is made to inhibiting the binding of both an immobilized antibody and a labeled mobile antibody by the presence of an autoantibody. A meaningful correlation of autoantibody present in the test sample would not be obtained if the teaching were modified into a test strip format. The issue is not whether the complex of Bergman would or would not migrate along the test strip, but that Bergman does not disclose a test tube assay corresponding to the embodiment of Applicant's invention as defined in claims 168 and 198 that might have been suitable for modification into a test strip format and which would enable the detection of autoantibodies.

Bergman does not disclose or teach autoantibody detection by synchronous competitive inhibition of antibody binding at more than one binding site of the antigen. In particular, Bergman does not disclose or teach a method wherein first and second autoantibodies respectively competitively inhibit binding of an immobilized antibody and a free labeled antibody to distinct binding sites on the antigen. Bergman, where the inhibition of binding of both immobilized and free antibodies is envisaged, is quite different from Applicant's invention. Applicant's invention employs an immobilized first antibody and a free labeled second antibody, where the immobilized and free (non-immobilized) antibodies respectively bind distinct first and second binding sites on the antigen (not a common binding site). This binding with the distinct binding sites is competitively inhibited by first and second autoantibodies.

If a test strip assay were provided by modifying the teaching of Bergman into test strip format, with both the immobilized antibody and the labeled non-immobilized antibody binding a common binding site of the antigen as required by the teaching of Bergman, then the resulting test strip assay would not be suitable for the detection of autoantibodies. In such an assay, the labeled free antibody, immobilized antibody and analyte autoantibody would compete for binding to a common binding site on the antigen and this would not allow for a competitive assay where binding of the labeled antibody to the test strip (via the antigen – immobilized antibody) could provide a meaningful correlation as to the presence of autoantibody or autoantibodies in a test sample. The M.P.E.P. states that "[i]f a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." M.P.E.P.§ 2143.01 at 2100-127. Clearly, this is such an instance. If the Bergman reference were modified in the way suggested by the Examiner, the resulting test strip assay would not be suitable for the detection of autoantibodies. See Figure 1 for a description of the competitive binding as envisaged by Bergman and modified for use in a test strip as suggested by Examiner.

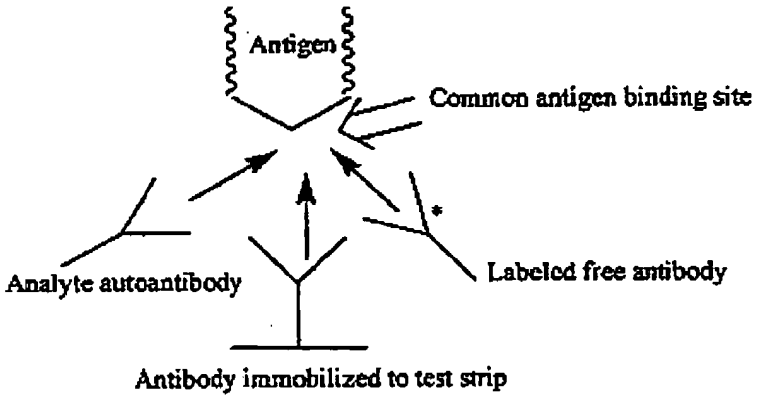

Figure 1. Competitive binding as envisaged by Bergman and modified for use in a test strip as suggested by Examiner.

Applicant's invention, on the other hand, does allow a meaningful correlation to the presence of autoantibodies in a test sample. See Figure 2 for an illustration of Applicant's invention.

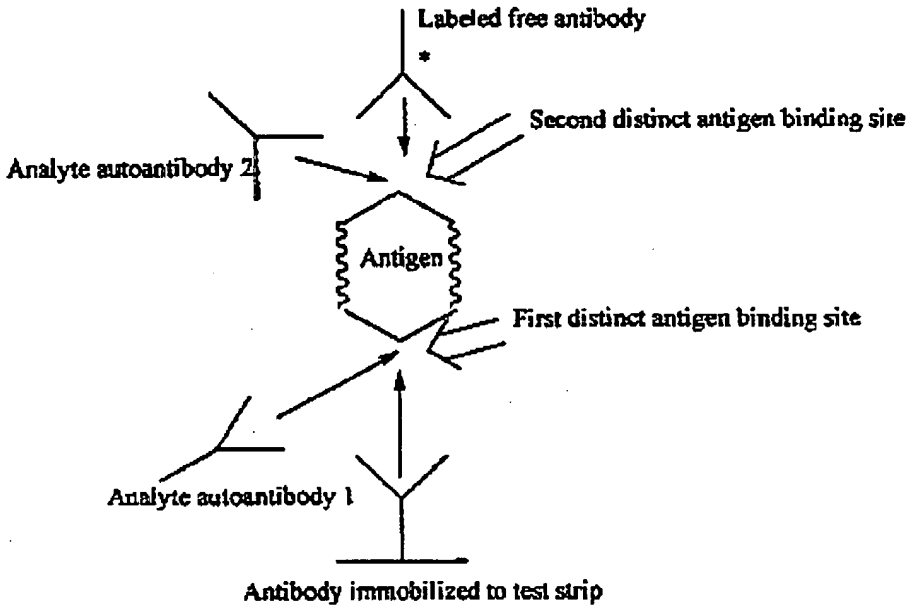

Figure 2. Illustration of Applicant's invention, which does allow for a meaningful correlation as to the presence of autoantibodies in a test sample

Claims 168 and 198 provide, via the provision of an immobilized first antibody and a labeled non-immobilized second antibody binding to distinct binding sites on the antigen, a rapid and sensitive detection of autoantibodies. This clearly provides advantages over and above the teaching of Bergman.

The reliance on May and Ehrenkranz does not remedy the defects of Bergman. Ehrenkranz describes an immunoassay for TSH which comprises a substrate (such as a strip) divided into four, or optionally five regions, where:

(i) the first is a reservoir for accepting a sample of human blood;

(ii) the second is a region coated with unbound, labeled antibody that has been selected for its high affinity to an epitope of TSH;

(iii) the third is a region containing a second antibody bound to the substrate, which has been selected for its high affinity to an epitope (which would need to be different to that recognized by the antibody of (ii) for detection to occur) of TSH;

(iv) the fourth is a control reagent that either binds to labeled antibody or changes color when hydrated; and

(v) the last, which is optional, is a sink that absorbs any liquid that has migrated along the substrate from the reservoir.

In other words, in the assay of Ehrenkranz, sample TSH reacts with mobile antibody and both are transported to the bound antibody so as to form a sandwich complex therewith. This is a non-competitive sandwich assay, which relies on the mobile and bound antibodies interacting with different epitopes on the TSH to allow the formation of the sandwich complex.

This is quite different from the assay of claims 168 and 198. First, Applicant's assay as defined in claims 168 and 198 relies on a competitive assay system, with sample autoantibodies competing with the immobilized and non-immobilized antibodies in the interaction with the mobile antigen. Ehrenkranz on the other hand is concerned with a non-competitive sandwich assay. Second, analyte TSH in Ehrenkranz interacts with the bound antibody to allow the formation of the sandwich complex. The analyte in Applicant's assay, namely autoantibodies, interacts with the mobile antigen. Third, in the presence of analyte TSH in the assay system of Ehrenkranz, a visible spot is formed in the stationary phase of the test strip due to the TSH interacting with the bound antibody and the labeled mobile antibody to form the above described complex. In Applicant's assay as defined in claims 168 and 198 formation of bound complex is inhibited in the presence of analyte autoantibody. Fourth, nothing in the teaching of Ehrenkranz envisages a system where synchronous detection of first and second analyte populations is achieved.

The respective assay systems of Applicant's invention (as defined in claims 168 and 198) and Ehrenkranz's TSH assay clearly employ different binding techniques. Thus, the combination of Bergman and Ehrenkranz does not disclose all of the elements, there is no suggestion of a motivation to combine or modify to obtain all of the elements,

and there is no reasonable expectation of success even if there were a motivation to combine and/or modify. See Figure 3 for a demonstration of the differences between Applicant's assay and the Ehrenkranz assay.

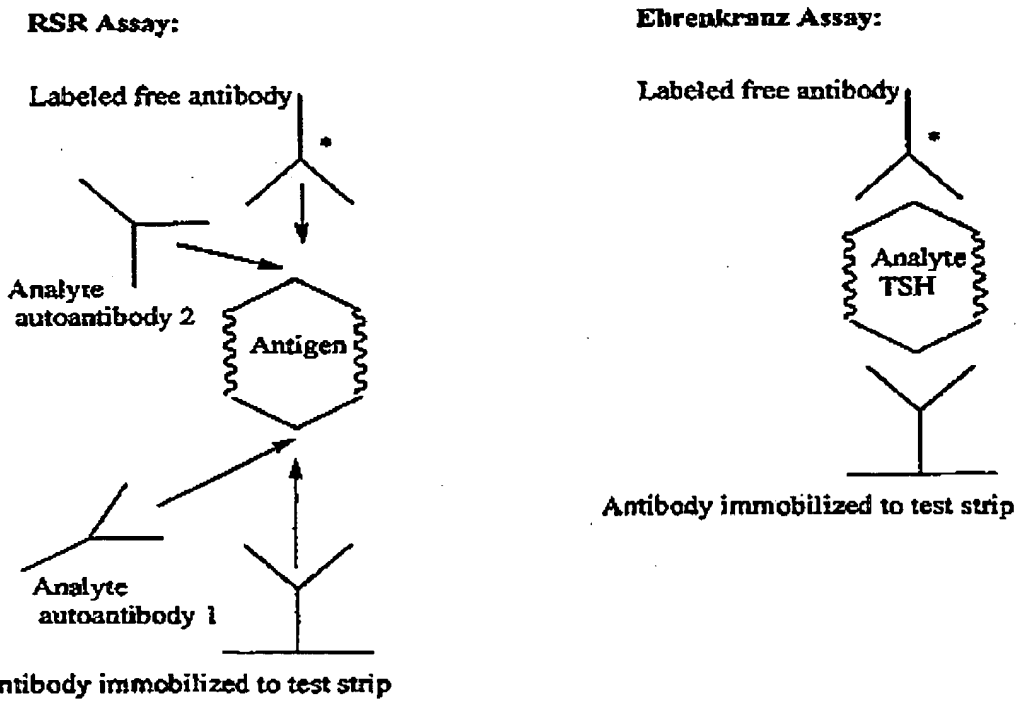

Figure 3: Demonstration of the differences between Applicant's assay and the Ehrenkranz assay.

These differences can be summarized as follows:

1. Applicant has a competitive system; Ehrenkranz does not.

2. Applicant analyte autoantibodies interact with mobile antigen and not immobilized "capture reagent"; Ehrenkranz analyte TSH interacts with bound antibody.

3. The presence of analyte autoantibody in Applicant's assay inhibits formation of bound complex; there is no inhibition of binding in the presence of analyte TSH in Ehrenkranz - to the contrary, sandwich complex forms on strip in the presence of analyte TSH.

4. Applicant's system allows synchronous detection of analyte autoantibodies 1 and 2; Ehrenkranz does not teach synchronous detection of analytes.

May also does not remedy the defects of Bergman and Ehrenkranz. May teaches a non-competitive assay where a liquid sample containing the analyte permeates a first detection zone including a labeled, mobile binding reagent which then binds the analyte and migrates therewith to the second detection zone. A complex is then formed with the immobilized binding reagent present in the second zone. May clearly explains that the two binding reagents have specificities for different epitopes of the analyte. The system described by May employs the same assay binding techniques as disclosed by Ehrenkranz. However, May is directed to the detection of hCG and Ehrenkranz is directed to the detection of TSH. May suffers from the same defects as Ehrenkranz. The combination of the references do not disclose all of the elements, there is no suggestion of a motivation to combine or modify the references to obtain all of the elements, and there is no reasonable expectation of success even if one were motivated to combine and/or modify.

Test tube incubation assays were known in the art from Bergman. Test strip assays were known from May and Ehrenkranz. None of the test tube assays of Bergman correspond to, disclose, or suggest a binding system as employed in an assay according to claims 168 and 198. Although test strip assays are well known in the art, neither May or Ehrenkranz suggest an assay system for their respective analytes employing binding techniques according to the present invention.

There is no motivation to combine the cited references and no reasonable expectation of success. Bergman represented the level of skill in the art at the time of invention for the detection of autoantibodies, where assay systems suitable for test tube incubation are disclosed. Prior to Applicant's invention there was no disclosure as to what assay systems for autoantibodies may or may not have been suitable for use in test strip format. Test tube incubation assays as represented by Bergman were thus the extent of the assay systems employed and known to be useful in the detection of autoantibodies at the priority date of the present invention, and in the context of autoantibody detection these test tube incubation assays would have represented the level of skill in the art at the priority date. An addressee motivated to detect autoantibodies in test strip format might have considered modifying one of the specific embodiments of Bergman into test strip format, but there was no teaching in Bergman that would have lead one of skill in the art

to an assay system as defined in claims 168 and 198. A person skilled in the art considering Bergman, May, and Ehrenkranz would not have arrived at the Applicant's invention as defined in claims 168 and 198, considering what was known in the field of immunology prior to Applicant's invention. Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 168 and 170-181 under 35 U.S.C. §103(a).

With respect to the rejection of claims 198 and 200-210, which were rejected under 35 U.S.C. § 103(a) as obvious over Bergman in view of Ehrenkranz, and May et al. as applied to claims 154-168, 170-181, and 211-212, and further in view of Foster et al. Applicant respectfully asserts that Foster fails to remedy the shortcomings of Bergman, Ehrenkranz and May. Applicant therefore respectfully requests that the Examiner withdraw this rejection.

Rejection of Claims 154-167, 184-197, and 211 under 35 U.S.C. § 103(a)

Claims 154-167 and 212 are rejected under 35 U.S.C. § 103(a) as obvious over Bergman in view of Ehrenkranz and May et al. Claims 184-197 are rejected under 35 U.S.C. § 103(a) as obvious over Bergman in view of Ehrenkranz and May et al. as applied to claims 154-168, 170-181, and 211-212, and further in view of Foster et al. Applicant respectfully traverses these rejections and submits that the claims are not obvious in light of the cited references.

Amended independent claims 184 and 211 represent kit and method claims respectively where first and second antibodies are immobilized on the test strip, which recognize first and second binding sites on a common antigen. These claims have been amended to remove the "and / or" language as objected to by the Examiner, and also to clarify that the immobilized antibodies are provided at discrete positions on the test strip so as to enable detection and identification of first and second populations of autoantibodies to the antigen. Claims 154-167 are dependent on 211, and claims 185-197 are dependent on claim 184.

As discussed above in detail, Ehrenkranz teaches a sandwich complex comprising an immobilized antibody, TSH and labeled antibody (and as such multivalent binding to TSH), to form a sandwich complex. This is quite different from the use of first and

second immobilized antibodies allowing the detection of distinct autoantibody populations on a test strip as defined in claims 184 and 211. Indeed, given that Ehrenkranz is directed to the detection of a single analyte, namely TSH, it would have been contrary to the teaching thereof to modify the TSH test strip to include two detection zones. Because Ehrenkranz teaches away from the modification, there is no motivation to combine or suggestion of success.

Furthermore, as explained above, Ehrenkranz is directed to a non-competitive assay system and again a kit and method as defined in claims 184 and 211 relies on competitive binding techniques. See Figure 4 for the differences between the Applicant's invention and the TSH test strip of Ehrenkranz.

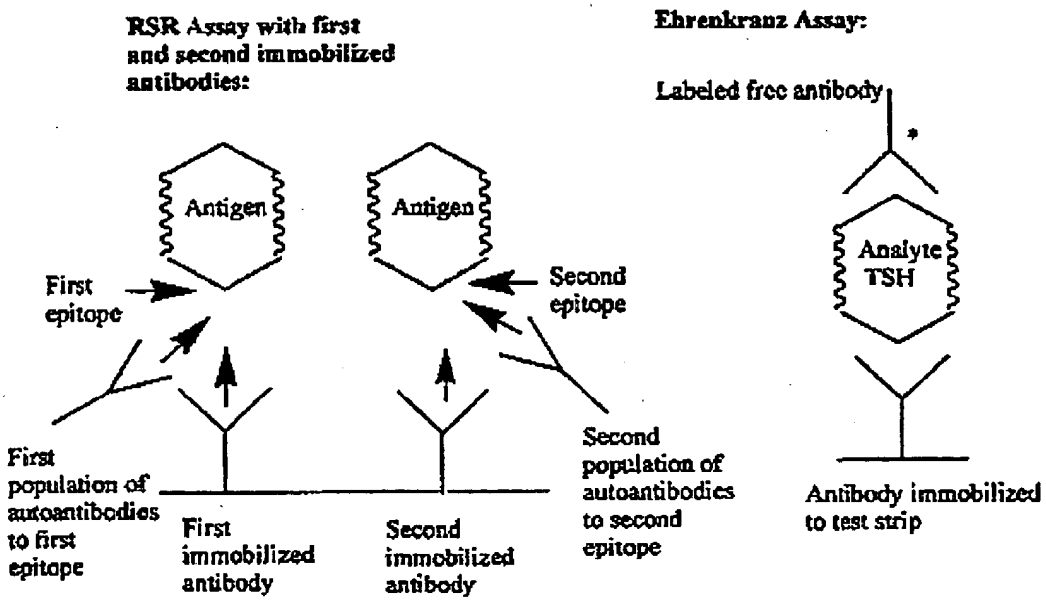

Figure 4: Demonstration of the differences between the Applicant's invention and the TSH test strip of Ehrenkranz.

A kit and method as defined in claims 184 and 211 would not have been reached considering the scope and content of the prior art, and taking into account the level of skill in the art. Considering the test tube incubation assays of Bergman, the idea of detecting first and second analytes would have been meaningless in the context of the test tube conditions employed, given the inability to detect and distinguish between different

analytes under such conditions. Considering the very different assays disclosed in both May and Ehrenkranz compared to Applicant's invention, the disclosure of these documents is essentially only relevant to show the known use of test strips in the art. The fact that multivalent antigens are employed in the test strip of Ehrenkranz does not suggest the techniques now employed by Applicant. Again, for claims 184 and 211, the teaching of Ehrenkranz does not indicate obviousness over and above the teaching of Bergman and May, in view of the respective teachings of these documents, as discussed in detail above. Thus there is no suggestion of a motivation to combine or modify, and there is no reasonable expectation of success.

As discussed above, Bergman represented the level of skill in the art at date of invention for the detection of autoantibodies, where assay systems suitable for test tube incubation are disclosed. Prior to Applicant's invention there was no disclosure as to what assay systems for autoantibodies may or may not have been suitable for use in test strip format. Test tube incubation assays as represented by Bergman were the extent of the assay systems employed and known to be useful in the detection of autoantibodies at the priority date of the present invention. Thus, neither the test tube assays of Bergman, nor the test strips of May and Ehrenkranz, would have provided any meaningful teaching as to the use of first and second immobilized antibodies as now employed in Applicant's invention and covered by claims 184 and 211. There is no suggestion of a motivation to combine or modify, and there is no reasonable expectation of success. Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 154-167, 184-197, and 211 under 35 U.S.C. §103(a).

Rejection of Claim 212 under 35 U.S.C. § 103(a)

Claim 212 is rejected under 35 U.S.C. § 103(a) as obvious over Bergman in view of Ehrenkranz and May et al. Applicant respectfully traverses these rejections and submits that the claims are not obvious in light of the cited references.

Amended claim 212 and proposed new independent claims 215 and 216 represent method and kit claims where first and second antibodies are immobilized to the test strip and first and second distinct antigens are employed. Again, these claims have been amended to remove the "and / or" language as objected to by the Examiner and also to

clarify that the immobilized antibodies are provided at discrete locations on the test strip so as to enable detection and identification of first and second populations of autoantibodies recognizing distinct antigens.

As discussed above in detail, Ehrenkranz teaches a sandwich complex comprising an immobilized antibody, TSH and labeled antibody (and as such multivalent binding to TSH), to form a sandwich complex. This is quite different from the use of first and second immobilized antibodies respectively directed to first and second distinct antigens thus allowing the detection of distinct autoantibody populations to different antigens on a single test strip. The differences between Applicant's invention and the TSH test strip of Ehrenkranz are demonstrated in Figure 5.

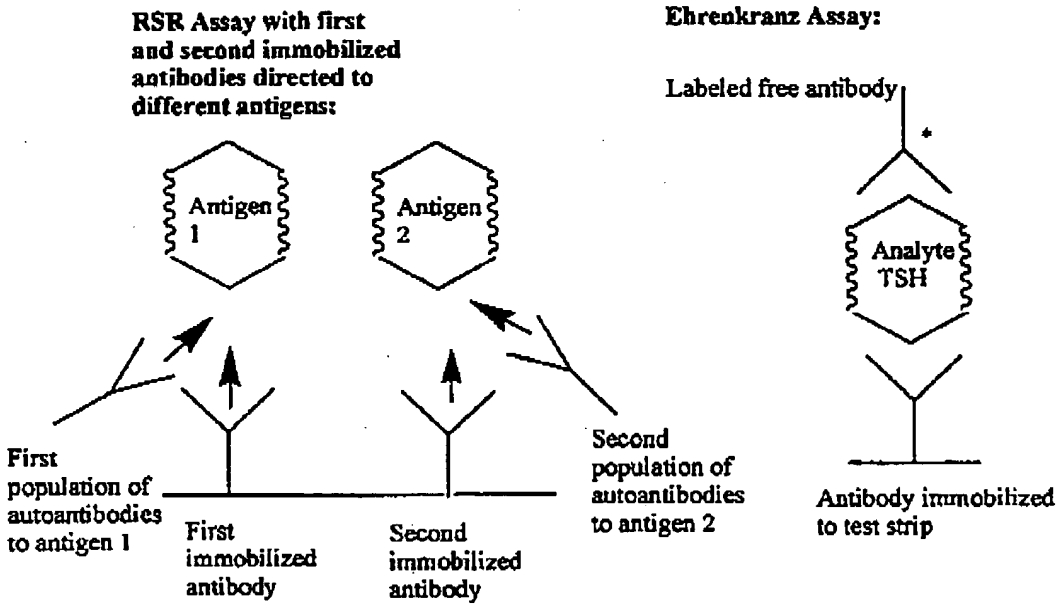

Figure 5: Demonstration of the differences between the Applicant's invention and the TSH test strip of Ehrenkranz.

A kit and method as defined in claims 212, 215, and 216 would not have been reached considering the scope and content of the prior art, and taking into account the level of skill in the art. First, considering the test tube incubation assays of Bergman, as

explained above, the idea of detecting first and second analytes would have been meaningless in the context of the test tube conditions employed, given the inability to detect and distinguish between different analytes under such conditions. As discussed above for claims 184 and 211, the fact that multivalent antigens are employed in the test strip of Ehrenkranz is in no way suggestive as to the techniques now employed by Applicant. Again for claims 212, 215, and 216 the teaching of Ehrenkranz does not remedy the defects of Bergman and May. There is no suggestion of a motivation to combine or modify, and there is no reasonable expectation of success.

The level of skill in the art at the date of invention for the detection of autoantibodies was, as discussed above, represented by Bergman. Under Bergman, the detection of autoantibodies at that time was restricted to test tube incubations, in the context of which detection of autoantibodies to first and second antigens could simply not have been envisaged. Thus, neither the test tube assays of Bergman, nor the test strips of May and Ehrenkranz, would have provided any meaningful teaching as to the use of first and second immobilized antibodies as now employed in Applicant's invention and covered by claims 212, 215, and 216. There is no suggestion of a motivation to combine or modify, and there is no reasonable expectation of success. Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claim 212 under 35 U.S.C. §103(a) and allow claims 215 and 216.

CONCLUSION

To make out a *prima facie* case of obviousness under 35 U.S.C. § 103(a), there must exist some motivation, either generally available to one of ordinary skill in the art or expressly stated in the prior art, to modify the known prior art to arrive at the claimed invention. Examiner has failed to state a motivation generally available to one skilled in the art to modify the cited prior art to obtain the claimed invention. Additionally, the cited prior fails to articulate such a motivation. Thus, Bergman, Ehrenkranz, May et al., and Foster et al. cannot serve as a proper basis for a rejection under 35 U.S.C. § 103(a). In view of the above comments, it is submitted that a *prima facie* case of obviousness has not been established. For the foregoing reasons, Applicant respectfully requests that the

Examiner withdraw the rejection of claims 154-168, 170-181, 184-198, and 200-212 under 35 U.S.C. §103(a).

Claims 154-168, 170-181, 184-198, 200-212, and 215-216 remain pending in the application. All claims are believed to be allowable for the reasons set forth above. Early notice to this effect is earnestly solicited. This amendment is believed to be responsive to all points raised in the Office Action. There may be additional reasons to allow the claims and Applicant reserves the right to raise them at a later date. Accordingly, Applicant respectfully requests reconsideration, allowance, and passage of the application to issue. If the Examiner has any questions or concerns, please feel free to contact the undersigned.

Respectfully submitted,

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Dated: February 24, 2004

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